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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 08/182,621 | 01/13/94 | ENGELHARDT D | ENZ52 |

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| EXAMINER | |
|---|---|
| REES, D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1807 | |

DATE MAILED: 04/09/97

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/182,621 | Applicant(s) Engelhardt et al. |
|---|---|---|
| | Examiner Dianne Rees | Group Art Unit 1807 |

☒ Responsive to communication(s) filed on *7/3/96, 10/1/96* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-90* is/are pending in the application.

Of the above, claim(s) *52-72 and 81-90* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-51 and 73-80* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-90* are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Election/Restriction*

1. Applicant's election with traverse of Group I, claims 1-51 and 73-80 in Paper No. is acknowledged. The traversal is on the ground(s) that the claims represented by Groups I,II and III "form a single inventive concept which should be properly examined in the same application". Applicant's contend that a diligent search of the art for any of these groups would necessitate a review of the art --at least in part for the other corresponding groups. This position is particularly supported by the fact that each of the claim groups are classified in Class 435." Applicant's arguments are considered but are not deemed persuasive. The subclass distinctions between the classes require a completely different search strategy for each group. Further the examiner merely listed exemplary classification for the different groups; Group II additionally falls within Class 536 Subclass 23.1, and Group III additionally falls within Class 530 subclass 300. Thus while a search for any one group may overlap with a search for another group , the searches would not be coextensive and a reference that would render the invention of one group obvious would not necessarily render the invention of another group obvious. Accordingly as the inventions are patentably distinct and the burden of search is undue, the requirement is still deemed proper and is therefore made FINAL.

*Specification*

2. The disclosure is objected to because of the following informalities: The specification contains illustrations that should be provided separately as Figures (see for example page 30) as curved lines will not be able to be reproduced by the printing process.

Appropriate correction is required.

*Claim Rejections - 35 USC § 112*

3. Claims 73-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to an in vivo process of producing a specific nucleic acid which comprises a conjugate comprising a protein nucleic acid construct, the conjugate is defined solely by the functional limitation of being "capable of producing a nucleic acid when present in a cell" and introducing the conjugate in the cell. In further embodiments of the invention the construct "codes for the protein in said conjugate" or other than the protein in said conjugate. In claim 78, the "other protein" is recited as a nucleic acid polymerase. The claims include any type of protein imaginable to be linked by any means to the conjugate such that the conjugate may be capable of producing a nucleic acid when present in a cell. The ability of

promoters drive transcription of a sequence and thereby produce a specific nucleic acid is well known in the art. Additionally a large number of replication competent vectors are known in the art that may produce more copies of a nucleic acid in vivo and in vitro; however, the specification discloses that the conjugates are to specifically contain either an RNA or DNA polymerase conjugated to the construct through a linkage group "not substantially interfereing" ith its funtion and does not disclose any other type of protein envisioned. Furhter, no teachings of other types of proteins that may replicate a nucleic acid molecule is provided, and even for those constructs in which polymerases are taught there is no teaching of what types of linkages would not substantially interfere with the function of a polymerase. Given that the art teaches that a polymerase must translocate along its template if acting processively, the art raises doubts that a polymerase tethered to an oligonucleotide may actually replicate that oligonucleotide. Given that the specification provides no guidance as to which of the large genus of proteins claimed as being conjugated to an oligonucleotide would be likely to function in such a method, and given the doubts raised by the art and the unpredictability of the art , it is the position of the examiner that it would require undue experimentation to perform the method of the claims as broadly written.

4. Claims 1-51, 73-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 1 is indefinite in the recitation of "introduction of an intermediate structure" is as it is unclear what the "structure" refers to (a reagent which is introduced into the reaction mix?). The claim is further unclear in the recitation of "nucleic acid precursors" as it is unclear how "precursors" is defined (sugars? bases?). See all claims for examples of this language.

b) Claim 3 is indefinite in the recitation of "DNA.RNA" hybrid as the claim appears to intends --DNA:RNA-- hybrid. See also claim 14 and 42.

c) Claim 5 is indefinite in the recitation of "blunt end promoting" as the action of a restriction enzyme would seem to be all or none so it is unclear what is meant by "promoting".

d) Claim 7 is indefinite in the recitation of "sandwich or sandwich capture" as it is unclear how the terms are distinguished from each other.

e) Claim 8 is indefinite in the recitation of "said captured specific nucleic acid" as the term lacks proper antecedent basis in the claims.

f) Claim 18 is indefinite in the recitation of "not substantially complementary". "Substantially" is a relative term and therefore it is unclear what the metes and bounds of the nucleic acid primers are.

g) Claim 22 is indefinite in the recitation of "At least one sequence thereof" as it is unclear how sequence is being distinguished from a "nucleotide".

h) Claim 27 is indefinite int recitation of "modified by" as it is unclear if the term implies linkage to or the action of an intercalating agent on a primer for example.

I) Claim 30 is indefinite in the recitation of "regenerating said none or more" as it is unclear what "regenerating" refers to (reproducing the sequence? or providing the primer for use in subsequent amplification reactions?).

j) Claim 31 is indefinite in the recitation of "substantially complementary" (see above) and "distinct sequence" as it is unclear what criteria is used to determine whether a primer is "distinct " or not. See all claims for examples of his language.

k) Claim 47 is indefinite in the recitation of "one segment" as the claim appears to intend --one segment--. The claim is further indefinite in the recitation of the recitation of "at least one non-complementary sequence...such that upon hybridization ...at least one loop structure is formed" as it is unclear how a single mismatch can form an actual loop structure.

l) Claim 73 is indefinite in the recitation of "a protein -nucleic acid conjugate" as it is unclear what the nature of the conjugate is (a protein covalently linked to a nucleic acid? a protein associated with a nucleic acid?). It is further unclear under what conditions the conjugate is "capable of producing a nucleic acid when present in a cell" since step (b) suggests that the "introducing" step is actually the producing step. Claim 75 is indefinite in the recitation of :at least one complementary sequence to a primer present in the cell" in that it is unclear how complementary is defined (fully complementary? partially?) and further whether the primer present in the cell represents an endogenous sequence or one which was introduced into the cell.

m) Claim 76 is indefinite in the recitation of "said nucleic acid construct codes for the protein in said conjugate" . As above it is unclear what the exact relationship is between the protein and the nucleic acid is.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 10, 11,12,14 ,15,16, 18,20,21,22,23,24, 26,28,30 are rejected under 35 U.S.C. 102(b) as being anticipated by Aono et al. (JP 4-304900) .

Aono et al '900 teaches a method which comprises providing a single stranded circular template, an effective amount of an oligonucleotide primer. A single polymerase is used to catalyze the reaction; no auxiliary proteins are required. Four nucleotide triphosphates are provided (i.e at least 2) and the polymerase produces a single stranded oligonucleotide multimer comprising multiple copies of the oligonucleotide (i.e more than one copy of the target sequence) (As these multimers include the primer seuqences , it may be interpreted that this process 'regenerates" the primer). Aono further teaches that the target may be "fragmented".or digested with a restriction enzyme (and does not limit the type of restriction enzyme to be used to either

one that produces blunt ends or one that produces overhangs) and teaches that the primer has at least a partially complementary sequence (see pages 8-10, i.e may comprise at least one noncomplementary nucleotide, at least one may further be interpreted as "about 5") and Figure on page 16. Amplified nucleic acids are subsequently detected (in this example by gel electrophoresis (see page 18)). No intermediate structure is required to be formed and although denaturing and annealing occurs over a temperature range, the actual reaction of the mixture (primer, nucleic acid precursors, and nucleic acid producing catalyst) is performed isothermally (see for example page 14, of the '900 patent) at 75oC for 60 minutes and the buffer and ionic strength are unaltered while performing this reaction.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-4, 10, 11,12,14 ,15,16, 18,20,21,22, 26, 28,30 are rejected under 35 U.S.C. 102 (e) as being anticipated by Auerbach et al..

Auerbach et al (USPAT 534668, with a priority date accorded of Aug 24, 1992) teaches methods for amplifying a nucleic acid molecule which employs at least one primer sequence which may

hybridize to complementary sequences of a primer binding site. Among the polymerases that may be used in this method are T4 polymerase, T7 polymerase, T5 polymerase and Taq. Amplification may occur by a rolling circle method (see Figure 8a) and is performed under isothermal and isostatic conditions.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claim 73 is rejected under 35 U.S.C. 102(e) as being anticipated by Gerwitz.

Gerwitz (USPAT 5612212, filed Nov 12, 1993) teaches an in vivo process in which a conjugate comprising a protein-nucleic acid construct (see column 9, lines 46-70, and column 10, lines 1-10) is provided and introduced into a cell (since this step is recited as the means by which

the nucleic acid is produced in step(b) it is interpreted that the method of Gerwitz also "thereby produces said nucleic acid").

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4,6 10, 11,12,14 ,15,16,20,26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Watson et al.In Molecular Biology of the Gene, 1987.

Watson et al teaches in vitro processes to replicate DNA (i.e produce more than one copy of said DNA) by providing a nucleic acid sample, nucleic acid precursors, a nucleic acid producing polymerase wherein the reactions occur under isothermal, isostatic conditions, (i.e by providing cell extracts).

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 7-9, 13,17, 18,19, 25, 29,30, 31-36,37,38, 39-43,44, 45,46,47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aono in view of Auerbach, in view of Urdea (USPAT 5118605), in view of Gerwitz, and further in view of Backman et al

Aono et al. meets all of the limitations of the claims except for the teaching that the that the target DNA may be initially purified and that the purification method may be by a means of a sandwich capture assay, followed release of the nucleic acid via digestion by a restriction enzyme, that the primers or precursor nucleic acids may be labelled or otherwise modified nucleic acids, or that the primers used in the method may be regenerated such as by digestion with RNAse, or that the primers may contain an isosteric heteroatom at their 3' end. However, the practice of said methodology and the advantages that such methodology afforded was well known in the art at the time that the invention was made.

Auerbach, for example, teaches that a means of isolating nucleic acid moleucles may be via a sandwich assay using a capture oligonucleotide bound to a solid support which may be used to purify a target prior to amplification (see column 23) (Auerbach also teaches that the method may be used again subsequent to amplification to achieve increased sensitivity ,see column 24). Urdea teaches similar methodology which is further modified by the step of subsequently cleaving the captured nucleic acid from the probe by a restriction enzyme. (see Figure 2). Gerwitz teaches the advantages in incorporating modified nucleotides into nucleic acid such as

to enhance both hybridization efficiency and to enhance resistance to nuclease digestion (see column 3).. Backman et al. further discusses general methodology used in amplification techniques to regenerate primers.The technique comprises including a ribonucleotide residue into an otherwise deoxy ribonucleotide and the use of RNAse H or alkaline hydrolysis to liberate the primer from its extended template (see column 9).

It therefore would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to modify the method of Aono in view of the teachings of Auerbach, Gerwitz and Backman et al. to achieve the respective benefits taught by Auerbach in view of Urdea, and Gerwitz and Backman as being attainable by performing such methodology. One would be readily motivated to perform sandwich capture assays prior to an amplification step to achieve the expected benefit of being able to remove nontarget nucleic acids from target nucleic acids thus increasing the sensitivity of the amplification reaction. One would be motivated to subsequently remove the target from the support (either by cleavage or by elution) to capitalize on the advantages, well know to those in the chemical arts, of performing a reaction in solution rather than on a support. One would be motivated to incorporate modified nucleic acids in a sequence to promote its stability and to enhance its ability to hybridize as taught by Gerwitz and further, since Aono teaches that the primer sequences are to be at least partially complementary, one of ordinary skill in the art at the time that the invention was made would be equally motivated to modify either noncomplementary or complementary sequences or both, for the expected benefits of obtaining increased resistance to nuclease digestion. Similarly, one

would be motivated to obtain the benefits of increased efficiency in an amplification reaction given the teachings of Backmann that this may be effectively done by regenerating reagents required for this reaction (such as primers). Given the teachings of Beckman of the general advantages of providing a moiety at the 3' end of a primer that might be selectively cleaved to regenerate a primer, one would be motivated to substitute functional equivalents of such moieties. Urdea teaches that specific chemical groups that may be used to remove one sequence segment from another is a disulfide linkage . Therefore one of ordinary skill in the art at the time that the invention was made would have had a reasonable expectation of success in substituting a primer with a thiol group at its 3' end for the ribonucleotide modified primers taught by Beckman. The use of labelled primers or nucleotide precursors in such a technique would further have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made given that this methodology was routinely coupled to methods of detection of amplified sequences as a means of increasing the sensitivity of such an assay. Absent any evidence to the contrary, it would have been additionally prima facie obvious to one of ordinary skill in the art in view of the teachings of Aono to modify the number of complementary sequences to provide the maximum number required to allow for specific hybridization therefore the recitation of "no more" than 5 would have been prima facie obvious to one of ordinary skill in the art at time that the invention was as part of an effort to optimize the design of such sequences.

Claim 27 is allowable over the prior art.

No claims are allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800

3/31/97